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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/580,746	HOERR ET AL.	
	Examiner	Art Unit	
	MARIA B. MARVICH	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *18-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 May 2006* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/3/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to an amendment filed 6/5/09. Claims 1-20 are pending. Claim 20 has been withdrawn.

Election/Restrictions

Applicant's election with traverse of Group II (claims 1-17) in the reply filed on is acknowledged. The traversal is on the ground(s) that 1) there is no burden to search and examine the entire application and therefore it must be examined on its merits 2) the product and process claims should be examined together because they are acceptable combination of categories and 3) unity of invention was found in the International Search Report. This is not found persuasive because search burden is not the criteria in examination of National stage application; rather the legal standard is unity of invention. Furthermore, the ISR and IPER do not provide the guidance for examination of the National Stage application. Given the identification of art (listed below) that demonstrates that the claimed invention, Group I-IV do not form a single general inventive concept and lack unity. As to examination of product and process together, this combination of groups was indicated as related by inclusion of the standard under *in re Ochia* on page 4. However, in order to garner rejoinder of product and process claims, the product must have been elected and found allowable. Applicants have elected the process claims and hence rejoinder is not proper.

The requirement is still deemed proper and is therefore made FINAL.

It is noted that applicants' response is incomplete in that applicants did not elect a species of disorders or a specific cytokine. However, given the overlapping species identified in the art

as set forth below, the species requirements listed previously as well as for a tumor antigen are withdrawn.

Information Disclosure Statement

Documents listed on the IDS as International Search Reports have been considered but have been crossed out as PCT reports do not constitute documents under 367 CFR 1.98.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because: Non-initialed and/or non-dated alterations have been made to the oath or declaration. Specifically, the address of Dr. Hoerr has been altered. See 37 CFR 1.52(c).

Specification

The disclosure is objected to because of the following informalities: the heading, --Brief Description of the Drawings-- should be inserted in place of the phrase "Figures" between ¶ 3 and Figure 1 on page 42. MPEP 608.01(a). Appropriate correction is required

Drawings

Figures 1 is objected to under 37 CFR 1.83(a) because they fail to show any details as described in the specification. Specifically, figure 1 comprises a graph in the left panel and in the right panel microscopic images wherein the details of the right panels are indiscernible. Any structural detail that is essential for a proper understanding of the disclosed invention should be shown in the drawing. MPEP § 608.02(d). A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Claim Objections

Claims 1-17 are objected to because of the following informalities: Claims 1 and 2 have amended presentation of a. and b. to (a) and (b) except in line 1 of claim 2. It would be remedial for consistency to amend this occurrence. Claim 5 recites in the alternative "matrix M1 protein or influenza B matrix". It is improper in this claim as the Markush group language establishes a group wherein the proteins are not listed in the alternative. It would be remedial to omit the language "in particular" and "or" and include these two proteins within the listing. Similar amendment to claim 6 is required.

Each of claims 2-17 refer to the method of claim 1 and therefore it is improper to use the article "a" when referring to the method of claim 1. The article "a" or "an" refer to newly recited limitations.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 5 and 10-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: what leads to intensification or modulation of the immune response. While the claim indicates an outcome, it does not set forth how this outcome is achieved.

Regarding claim 5, the phrase "for example" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

It appears as if by the recitation that the mRNA is in the form of naked or complexed mRNA or in the form of globin UTR-stabilized mRNA is meant the mRNA is naked mRNA, complexed mRNA or globin UTR stabilized mRNA. To be in a form does not reflect that it is actually i.e. UTR stabilized mRNA.

Claim 10-15 recites the limitation "the modified mRNA" and/or "the wild-type RNA" in claim 1. There is insufficient antecedent basis for this limitation in the claim. For purposes of art, these claims will be considered to be dependent on claim 9

Claim 15 recites the limitation "the ribosome binding site" in claim 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 16 recites the limitation "the cationic or polycationic agent" in claim 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: is drawn to a method of claim 1 "for treatment" of tumour diseases" and etc. It appears as if the immune response is intended to treat a variety of disease. However, the claim does not indicate that the subject has this disorder nor what the relationship of the method is to the treatment plan. .

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-3, 5-9 and 12-17 are rejected under 35 U.S.C. 102(e) as being anticipated by Hoerr et al (US 20060188490; see entire document).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C.

102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15. A translation of PCT/EP05/009383is also required to ascertain that the designation that this application is a continuation of GER 102004042546.9.

Hoerr et al teach a method of transfecting cells with mRNA encoding antigens i.e. tumor antigens (see e.g. ¶ 0039 and 0046). The mRNA can be complexed to cationic polymer (see e.g. ¶ 0049). The antigen can be NY-Eso-1 (see e.g. ¶ 0018). The mRNAs are associated with stabilized UTRs i.e. globin (see e.g. ¶ 0024, 0034). The mRNA is administered with a cytokine such as IL-2 wherein the nucleotides comprise analogues (see e.g. ¶ 0035 and 0038). Administration is between 1 minute and 48 hours (See e.g. ¶ 0070).

Claims 1-9, 12-15 and 17 are rejected under 35 U.S.C. 102(e) as being anticipated by Terman et al (US 20050112141; see entire document).

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15. A translation of PCT/EP05/009383is also required to ascertain that the designation that this application is a continuation of GER 102004042546.9.

Terman et al as a whole provide teachings that demonstrate use of tumor antigen nucleic acid (i.e. mRNA, see e.g. table 1 and IV and example 34 and 35 especially ¶ 1258) with either cytokine or CpG or adjuvant RNA to enhance the immune response. For example, use of cytokine as an ISS is taught. "In the present invention, the ISS is inserted into nucleic acid sequences of SAgs and tumor associated antigens which are used to transfect tumor cells, antigen presenting cells, accessory cells including muscle cells in vitro or in vivo by methods given in Example 1-3, 15, 16, 18-23". ISS encompasses a number of cytokines (see e.g. ¶ 164-165). In another example, a string of bead of tumor antigens are prepared and introduced into Sag transfected cells or tumor cells and then treated with Dendritic cells. Terman et al teach that these cells are also activated by cytokine treatment (see e.g. ¶ 0049, 0053) and that CpG DNA is also introduced into the cell (see e.g. ¶ 0675). Furthermore, Sag nucleic acid addition can be considered an adjuvant RNA (nucleic acid is defined as DNA or RNA by Terman et al). For example (See ¶ 0376) "One approach to overcome the possible drawbacks of unfractionated tumor antigens is to use mRNA from tumor cells as a "source" of antigen. mRNA can be amplified from a very small number of cells, permitting the generation of sufficient amounts of antigen from minute amounts of tumor tissue Moreover, tumor-specific mRNA can be enriched by subtractive hybridization to remove RNA that is common to normal tissue. This increases the levels of the relevant tumor-specific antigen(s) that can be achieved, and hence, the potency of the vaccine. More importantly, this approach reduces the concentration of nonspecific antigens or, possibly, self-antigens, thereby lessening the potential for autoimmunity. Pulsing DCs with RNA is known to be effective in empowering them to induce CTL responses and tumor immunity." Administration of cytokines appears to follow 1 minute to 40 hours post nucleic acid

administration, (¶0392), Alternatively, they may be used to initiate adoptive T cell therapy by priming regional lymph nodes T cells which are harvested, expanded in vitro by stimulation with S/D/t cells, accompanied by, or followed with IL-2. The tumor antigen-sensitized T cells are reinfused into subjects as described in Example 29.Rnasin is used (see e.g. ¶ 1254). The compositions are administered naked or complexed (see e.g. ¶ 0940-0942). When preparing the mRNA, use of stabilized sequences such as globin is taught as well as used of analogues (see e.g. ¶ 492, 1249 and 1254). The length of the 5'UTR is minimized and furthermore, polyA sequences are found at the 3' end. Efforts are made to stabilize the mRNA i.e. addition of globin UTR and polyA form SV40 as well as mm-LDL use (see e.g. ¶ 0047 and 0441). It appears absent evidence to the contrary that destabilizing elements are not found in the sequences given these directives. As well, attachment of a ribosome binding site is taught (see e.g. ¶ 0074)

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Terman et al (US 20050112141; see entire document) in view of Draghia-Akli et al (US 7,316,925; see entire document) or Weiner et al (US 20020123099; see entire document).

Applicants claim a method for immunostimulation in a mammal by administration of at least one mRNA encoding at least one antigen of a tumor in combination with i.e. a cytokine or

CpG. The mRNA can be modified by increased GC content or increased AU content in the ribosome binding sequence.

The teachings of Terman et al are described above and are applied as before except the mRNA has not been modified by increased GC content or increased AU content in the ribosome binding sequence.

Draghia-Akli et al teach that a bias of GC content can increase mRNA stability (see e.g. ¶ 0067).

Weiner et al teach that the environment of the ribosome binding site is improved by an AT rich sequence (see e.g. ¶ 0062).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to improve mRNA stability according to the methods of Draghia-Akli and Weiner et al for the methods taught by Terman et al because Terman et al teach that it is within the ordinary skill of the art to use tumor antigens mRNA to modulate immune responses and that stable mRNA is preferred and because Draghia-Akli and Weiner et al teach that it is within the ordinary skill of the art to alter nucleotide content to improve the stability. In KSR International Co. v. Teleflex lnc., 82 USPQ2d 1385 (U.S. 2007), the Supreme Court particularly emphasized "the need for caution in granting a patent based on a combination of elements found in the prior art," (Id. At 1395) and discussed circumstances in which a patent might be determined to be obvious. Importantly, the Supreme Court reaffirmed principles based on its precedent that obviousness in part is predicated on use of particular known techniques that are recognized as part of the ordinary capabilities of one skilled in the art. In the instant case, it is accepted that generation of increased stability of mRNA is done by known methods in the art. As well, it is

within the ordinary skill of the art to use available methodologies to modify mRNA stability and one would have been motivated to do so in order as the ability do so by applying conventional methodologies. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARIA B. MARVICH whose telephone number is (571)272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Maria B Marvich, PhD

Primary Examiner
Art Unit 1633

/Maria B Marvich/
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